REMARKS

The present application is directed to a method of detecting the presence of a target nucleic acid in a sample. Prior to this Response, Claims 43-83, 85 and 86 were pending, with Claims 43-71 and 85-86 under examination and Claims 72-83 withdrawn from examination. In this Response, applicants amend Claims 43, 46, 48, 50, 53, 56-59, 62-63, and 65-67. Applicants cancel Claims 44-45, 47, 70-83 and 85-86 and add new Claims 87-88. The claim amendments do not add any new matter. Support for certain amendments to Claim 43 and for new Claim 88 is found, for example, in Claims 45 and 57-58, as previously presented. Support for certain amendments to Claim 66 and for new Claim 88 is found, for example, in Claim 70, as previously presented. Other claim amendments correct informalities and stylistic and typographical errors. After this Response, Claims 43, 46, 48-69 and 87-88 will be pending.

Claim Objections

The Examiner objects to Claim 71 under 37 C.F.R. §1.75(c) as being in improper form. Applicants cancel Claim 71, thereby rendering moot the objection.

Rejection of Claims under 35 U.S.C. § 112, First Paragraph, Written Description

The Examiner rejects Claims 43-70 and 85-86 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Applicants cancel Claims 44-45, 47, 70 and 85-86, thereby rendering their rejection moot. On page 6 of the Office Action, the Examiner cites the working examples in the application that describe the use of mitoxantrone and daunomycin. In an effort to facilitate allowance of the claims, applicants amend the pending claims to recite mitoxantrone, salts of mitoxantrone and daunomycin. Applicants assert that the claim amendments overcome the rejection of the claims pending after this Response. Applicants request withdrawal of the rejection.

Rejection of Claims under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner rejects Claims 43-70 and 85-86 under 35 U.S.C. § 112, first paragraph, for insufficient enablement. Applicants cancel Claims 44-45, 47, 70 and 85-86, thereby rendering their rejection moot. On pages 7 and 8 of the Office Action the Examiner states that the specification, while being enabling for the DNA binding agent being mitoxantrone and daunomycin, does not reasonably provide enablement for any other DNA duplex binding agents. In an effort to facilitate allowance of the claims, applicants amend the claims to recite mitoxantrone, salts of mitoxantrone and daunomycin. Applicants assert that the claim amendments overcome the rejection of the claims pending after this Response. Applicants request withdrawal of the rejection.

Rejection of Claims under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects Claims 43-70 and 85-86 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants cancel Claims 44-45, 47, 70 and 85-86, thereby rendering their rejection moot. On page 15 of the Office Action, the Examiner objects to the claim element "in the context of the method." In an effort to facilitate allowance of the claims, applicants delete the language "wherein emissions from the DNA duplex binding agent are not detectable in the context of the method" and amend the claims to recite specific DNA duplex binding agents, namely, mitoxantrone, salts of mitoxantrone and daunomycin. Applicants assert that the claims, as currently amended, are definite, and that the claim amendments overcome the rejection of the claims pending after this Response. Applicants request withdrawal of the rejection.

Rejection of Claims under 35 U.S.C. § 102(b)

Fisher

The Examiner rejects Claims 43-45, 47-55, 59-70 and 85-86 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,491,063 to Fisher *et al.* ("Fisher"). Applicants cancel Claims 44-45, 47, 70 and 85-86, thereby rendering their rejection moot. Applicants respectfully submit that the claim amendments overcome the rejection. MPEP 2131 provides: "To anticipate

a claim, the reference must teach each and every element of the claim." Applicants respectfully assert that Fisher fails to anticipate pending claims because it fails to teach at least one element of the claims.

Fisher discloses a method, in which an oligonucleotide labeled with a light-emitting label interacts in solution with a DNA-binding agent that quenches light emission from the label. The quenching occurs without hybridization of the labeled oligonucleotide to its complementary sequence and is sensitive to the length of oligonucleotide. The light emission from the label changes when the oligonucleotide cleavage occurs. *See* Fisher, column 3, line 55, through column 4, line 40. In other words, Fisher teaches a method, in which interaction between a DNA binding agent and a single-stranded oligonucleotide is monitored. *See* Fisher, column 4, lines 30-33.

The Examiner appears to assert on page 17 of the Office Action that Fisher anticipates currently pending claims by disclosing, for example, in column 4, line 44, through column 5, line 34, a method of detecting a target nucleic acid in a sample by hybridization to an oligonucleotide probe, which relies on selective cleavage of probes hybridized to target nucleic acid. Applicants respectfully bring to the Examiner's attention that, in Fisher, detection of cleaved probes indicates the presence of target nucleic acids. In contrast, the rejected claims, as currently amended, recite an element "wherein the probe is released intact from the target sequence." Accordingly, Fisher fails to teach at least one element of the claims, as pending after this Response, and fails to anticipate the claims for at least this reason. Applicants request withdrawal of the rejection.

Lee

The Examiner rejects Claims 43-44 and 48-69 under 35 U.S.C. § 102(b) as anticipated by Lee *et al.* (WO99/28500). Applicants cancel Claim 44, thereby rendering its rejection moot. Applicants respectfully assert that claim amendments overcome the rejection of the claims pending after this Response. Applicants amend the claims to incorporate the limitation of Claim 45. The claims, as currently amended, recite specific DNA duplex binding agents, namely, mitoxantrone, salts of mitoxantrone and daunomycin. Lee fails to teach mitoxantrone,

mitoxantrone salts or daunomycin, and also fails to teach using them as DNA duplex binding agents. Applicants respectfully assert that Lee fails to anticipate the amended claims because it fails to teach at least one element of the claims, namely, the DNA duplex binding agent. Applicants therefore request withdrawal of the rejection.

Rejection of Claims under 35 U.S.C. § 103(a)

Fisher in view of Smith

The Examiner rejects Claim 46 under 35 U.S.C. § 103(a) as obvious over Fisher in view of the article by Smith *et al.* "Mitoxantrone-DNA Binding and the Induction of Topoisomerase II Associated DNA Damage in Multi-Drug Resistant Small Cell Lung Cancer Cells", *Biochem. Pharma.* 1990, Vol. 40, No. 9, pp. 2069-2078 ("Smith"). The Examiner asserts that it would have been obvious to combine teachings of the cited publications in order to arrive at the rejected claim, as pending prior to this Response. *See* Office Action, pages 3-8. Applicants respectfully assert that a combination of Smith and Fisher fails to render obvious Claim 46.

MPEP 2142 states: "To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention 'as a whole' would have been obvious at that time to that person." Applicants respectfully assert that Claim 46 would not have been obvious to one of ordinary skill in the art in the field of the present application at its priority date. To reject a claim as obvious, the Examiner, first, must resolve the *Graham* factual inquires, namely, (a) determining the scope and content of the prior art, (b) ascertaining the differences between the claimed invention and the prior art, and (c) resolving the level of ordinary skill in the pertinent art. *See* MPEP 2141(II) citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

Applicants discussed Fisher in the previous section of this Response and Smith in the Second Amendment and Response to Office Action filed October 24, 2008 ("Previous Response"). *See,* for example, page 16 of the Previous Response. As discussed above, the

principle behind the method disclosed in Fischer is that a single-stranded oligonucleotide is cleaved, so that it is no longer available to interact with a DNA-binding compound that quenches a light-emitting label bound to the oligonucleotide. *See*, for example, Fisher, Abstract and column 4. It would not have been obvious to one of ordinary skill in the art in the area of the present application, at its priority date, to apply this system in any reaction, in which the single-stranded oligonucleotide (termed "oligonucleotide probe" in Fisher, for example in column 4, lines 44-59) is released intact from the target sequence, as recited in Claim 46, as currently amended.

Applicants respectfully assert that Smith fails to add to the knowledge of ordinary skill in the art gleaned from Fisher regarding methods of detecting nucleic acids. First, Smith fails to teach or suggest methods of detecting target nucleic acid sequences. Second, Smith does not teach or suggest using mitoxantrone for detecting target nucleic acid sequences. The Examiner asserts on page 27 of the Office Action that "mitoxantrone … was well known in the art at the time of the invention for use in fluorometic assays where donors and acceptors are used, as demonstrated by Smith." Applicants disagree.

Smith discloses the results of the study investigating the activity of mitoxantrone as a DNA-intercalating agent. *See,* for example, Smith, page 2070, first column, second paragraph. While Smith notes that mitoxantrone exerts a quenching effect on a particular dye, Ho33342, Smith uses this effect solely to hypothesize how mitoxantrone itself is interacting with DNA in a cell. For example, Smith states on page 2070, first column, lines 6-7, that the experimental data provides "preliminary information on the nuclear binding characteristics of mitoxantrone." Smith further teaches that differential binding of mitoxantrone to different cells allows for cell separation using flow cytometry. *See*, for example, Smith, page 2076, second column, last paragraph. On page 2076, Smith also teaches that mitoxantrone preferentially binds to some nucleic acid sequences.

Applicants respectfully assert that, based on the above teachings, one of ordinary skill in the art would not use mitoxantrone in an assay for detecting nucleic acids generally, since, in such an assay, reliable binding to any nucleic acid is a desirable parameter. Applicants further

assert that, based on the teaching in Smith, one of ordinary skill in the art in the area of nucleic acid detection methods would conclude that using mitoxantrone in such an assay would be problematic, since its preferential binding to some sequences would lead to variable results. Smith fails to teach or suggest that mitoxantrone can be used as a DNA duplex binding agent in a method for detecting target nucleic acid sequences, such as the claimed embodiment of applicants' method.

The Examiner also asserts on page 27 of the Office Action that Smith demonstrates that it was conventional in the art at the time of the invention to use mitoxantrone as a DNA intercalator and a fluorescence quencher, and concludes that it would have been obvious to substitute mitoxantrone for a DNA duplex binding agent in Fisher. Applicants respectfully disagree. Applicants discussed above why, based on the teaching of Smith on mitoxantrone preferential binding to some nucleic sequences, one of ordinary skill in the art in the area of the present application would think that mitoxantrone is an unsuitable agent for binding DNA duplexes in general.

Smith fails to suggest using mitoxantrone as a reagent in a method for detecting specific nucleic acid sequences. Rather, Smith is a scientific article describing a detailed investigation into the activity of mitoxantrone at the cellular level. In the course of the study disclosed in Smith, its authors discovered that, when cells containing mitoxantrone were stained with a particular dye, fluorescence from the dye was quenched in certain wavelengths. *See,* for example, Smith, Abstract. However, Smith fails to teach or suggest that mitoxantrone would be useful in an assay fore detecting specific target nucleic acid sequences.

The method disclosed in Fischer does not require the uses of an "intercalator," such as mitoxantrone, but rather involves the use of a DNA binding agent that interacts with single-stranded nucleotides. Accordingly, one of ordinary skill in the art in the area of DNA detection methods would not conclude, based on the disclosure of Smith, that mitoxantrone is an appropriate DNA binding agent for the methods disclosed in Fisher.

Based on the data disclosed in Smith, the authors of the study hypothesize that the observations of the quenching effect of mitoxantrone may be due to the "competition between

the intercalator and the minor groove ligand for binding sites on the DNA." *See* Smith, page 2076, first column, third paragraph. However, Smith fails to teach or suggest that mitoxantrone could act as a fluorescence quencher for use in methods where quenching is an effect of interaction between a donor and an acceptor, as in the method recited in the pending claims. To the contrary, if there was competition between mitoxantrone and a probe for DNA binding sites in the claimed embodiments of applicants' method, such competition would interfere with the method, since it would impede the close interaction of the donor and the acceptor that gives rise to the signal.

At least in view of the foregoing differences between the cited publications and the claims, applicants respectfully assert that Fisher or Smith, separately or in combination, fail to render obvious Claim 46. Applicants respectfully request withdrawal of the rejection.

Lee in view of Smith

The Examiner rejects Claims 45-47, 70 and 85-86 under 35 U.S.C. § 103(a) as obvious over Lee in view of Smith. Applicants cancel these claims, thereby rendering their rejection moot. Applicants request withdrawal of the rejection.

Applicants incorporated certain elements of the cited claims in the claims that will be pending after this Response. Applicants wish to assert that a combination of Lee and Smith fails to render obvious the claims, as currently amended, at least due to the reasons set forth on pages 14-17 of the Previous Response in the section "Rejection over International Publication WO 99/28500 in view of Smith et al." The Examiner indicates on pages 3-4 of the Office Action that applicants' arguments set forth in the Previous Response were persuasive.

Fisher in view of Lee

The Examiner rejects Claims 56-58 under 35 U.S.C. § 103(a) as obvious over Fischer in view of Lee. Applicants respectfully assert that a combination of Fischer and Lee fails to render obvious Claims 56-58. Fisher is discussed above. Lee discloses a method for detecting the presence of a target nucleic acid sequence in a sample using, among other things, a DNA duplex binding agent. Applicants discussed Lee on pages 14-15 of the Previous Response. In summary,

Lee addresses the unresolved problem of "signal leakage" by a different approach than applicants' methods disclosed in the present application and recited in the pending claims, which employ suitable DNA duplex binding agents. In contrast, Lee addresses the problem of "signal leakage" by seeking pairs of donor and acceptor molecules that each produce sharp signal peaks and have little or no overlap in emissions.

Applicants respectfully assert that combining the disclosure of Fisher regarding a method, in which interaction between a DNA-binding agent and a single-stranded oligonucleotide is monitored, with the disclosure in Lee does not suggest to one of ordinary skilled in the art Claims 56-58, which recite specific DNA duplex binding agents. Applicants therefore assert that, at least due to the foregoing differences between the disclosure of Fisher and Lee and Claims 56-58, a combination of Fisher and Lee fails to render obvious the rejected claims. Applicants request withdrawal of the rejection.

Rejection of Claims for Reasons of Nonstatutory Obviousness-Type Double Patenting

The Examiner rejects Claims 43-70 and 85-86 on the ground of nonstatutory obviousness-type double patenting as unpatentable over Claims 1, 2, 4-9 and 11-13 of U.S. Patent 6,833,257 (commonly owned with the present application and claiming the benefit of priority of Lee) in view of Smith. The Examiner states that, although the conflicting claims are not identical, they are not patentably distinct from each other because of a genus:species relationship. Applicants cancel Claims 44-45, 47, 70 and 85-86, thereby rendering their rejection moot.

Applicants respectfully traverse the rejection of the claims pending after this Response. Applicants respectfully bring to the Examiner's attention that arguments against a nonstatutory obviousness-type double patenting rejection of claims over U.S. Patent 6,833,257 in view of Smith were set forth on pages 18-19 of the Previous Response and found persuasive by the Examiner on page 4 of the Office Action. Applicants request clarification whether or not the arguments were persuasive.

Applicants respectfully submit that, under the judicially created doctrine of obviousness-type double patenting, the rejected claims are patentably distinct from Claims 1-2, 4-9 and 11-13 of U.S. Patent No. 6,833,257 in view of Smith at least because the emissions of the DNA duplex binding agents recited in the pending claims are not detectable in the context of the claimed methods. In the claimed methods, the DNA duplex binding agent is an acceptor, specifically selected so that during the course of the method it does not emit a signal, which interferes with that of a label, a part of a fluorescently labeled probe. The cited claims of U.S. Patent No. 6,833,257 do not teach or suggest DNA duplex binding agents recited in the pending claims and do not suggest using them in the methods, as recited in the pending claims.

The teaching of mitoxantrone in Smith does not remedy the deficiency of the cited claims of U.S. Patent No. 6,833,257 at least for the reasons stated above in the section discussing rejections involving Smith. Accordingly, applicants assert that Claims 1-2, 4-9 and 11-13 of U.S. Patent No. 6,833,257, separately or when taken in view of Smith, do not render obvious the rejected pending claims, which are therefore patentably distinct from the cited claims of U.S. Patent No. 6,833,257. Applicant requests withdrawal of the rejection.

CONCLUSION

This response fully addresses the rejections in the Office Action of March 18, 2009. In light of the above remarks, applicants respectfully assert that the application is now in condition for allowance. Such action is respectfully requested.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or if there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited. No additional fees are believed due; however the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account number 11-0855.

Respectfully submitted,

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